Hyperosmotic low-volume bowel preparations: Is NER1006 safe?

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Author contributions: Rex drafted the manuscript

Conflicts of Interest: Rex has received honoraria from Salix Pharmaceuticals and Braintree Laboratories

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This is the author's manuscript of the article published in final edited form as:

Rex, D. K. (2018). Hyperosmotic low-volume bowel preparations: Is NER1006 safe? Gastrointestinal Endoscopy. https://doi.org/10.1016/j.gie.2018.11.009

Dear Editor,

Recently, the U.S. Food and Drug Administration (FDA) approved the bowel preparation NER1006, marketed in the United States as Plenvu (Salix Pharmaceuticals, Bridgewater, NJ). Three randomized trials compared NER1006 to oral sulfate [1] (Suprep; Braintree Laboratories, Braintree, Mass), PEG-ELS plus ascorbate [2] (Moviprep; Salix Pharmaceuticals, Bridgewater, NJ), and sodium picosulfate/anhydrous magnesium citrate [3] (Prepopik; Ferring Pharmaceuticals, Parsippany, NJ). NER1006 is administered in only 1000 mLs of active ingredient. The total recommended minimum fluid intake with NER1006 is 2000 mL, making it the lowest total volume commercially available preparation in the United States. [1-3] A unique feature of NER1006, which the FDA apparently considered clinically insignificant, was an unprecedented incidence of hypernatremia.

Table 1 shows the randomized trials of NER1006 by their company assigned names. NER1006 was dosed as evening before dosing, split dosing (one dose in the evening and one in the morning), or both doses in the morning (Table 1). Two trials reported the incidence of abnormal serum electrolytes immediately before colonoscopy. Both serum sodium and chloride increased after NER1006 (Table 1). One trial (DAYB) did not report electrolyte changes. In NOCT the median increase in serum sodium at Visit 2 was 4.0 mmol/L for NER1006 versus 0.0 mmol/L for oral sulfate solution. In NOCT the incidence of serum sodium above the upper limit of normal was 9.4 times higher than oral sulfate solution (Table 1). In MORA an elevated serum sodium level with split-dose NER1006 occurred 7.5 times more frequently than with PEG-ELS plus ascorbate, and 9.4 times higher with morning only dosing. Electrolyte abnormalities after NER1006 were transient and considered not clinically significant. However, in the 3 trials

combined, 14 patients developed clinical dehydration with NER1006, compared with 2 patients in the comparator arms (1.4% vs 0.2%). Vomiting occurred in 51 patients receiving NER1006 vs 8 patients in the comparator arms (5.0% vs 1.0%).

Review of 3 trials of oral sulfate solution that include all of the other commonly prescribed FDA approved bowel preparations, including MoviPrep, Prepopik and 4 liter PEG-ELS (NuLYTELY: Braintree Laboratories, Braintree, Mass), confirms that the NER1006 incidence of hypernatremia is unprecedented. Hypernatremia and clinical dehydration appear clearly increased with NER1006. Hypernatremia may reflect large amounts of sodium ascorbate (48.11 grams in the second dose) and sodium sulfate in NER1006 plus insufficient free water intake. The more frequent occurrence of dehydration with NER1006 in the trials indicates this effect is clinically important. Outside of trials, where patients are often not as healthy as trial volunteers, and in elderly patients with limited thirst response, the dehydration risk should be expected to increase. That the electrolyte disturbances in the NER1006 trials reversed by the visit after colonoscopy is not reassuring, because adverse events from electrolyte disturbance would occur on the day or night of preparation.

After publication of NOCT, I discussed the incidence of hypernatremia with NER1006 in Journal Watch Gastroenterology [7]. Subsequently, the manufacturer engaged me, and acknowledged the need to encourage clear liquid intake beyond the prescribed 1 liter of required additional clear liquids. The following was added to the language in the "Important Safety Information" regarding Plenvu: "It is important to drink sufficient clear liquids before, during and after the use PLENVU. Be sure to consume additional clear liquids after the first and second dose of PLENVU." Also, the manufacturer commissioned an evaluation by a nephrologist, who

also identified concerns about hypernatremia, and made clinical recommendations (reproduced in Table 2 by permission of Salix Pharmaceuticals; Howard Franklin). Thus, the manufacturer has taken steps to address the risk of hypernatremia. Nevertheless, NER1006 continues to be marketed (http://www.plenvuhcp.com) as "Plenvu delivered a powerful bowel cleanse, with 33% less total fluid." Effective preparation for colonoscopy results in average fecal effluent volume of 2.5-3 liters [8-9]. NER1006 produces similar volumes of effluent [9], making it seem unwise to emphasize a reduced total fluid intake because a reduced intake volume may not compensate for fecal losses. A recommendation to take the active ingredient in NER1006 (1 liter) plus an additional 2 liters of water or clear liquid to avoid hypernatremia and dehydration seems appropriate.

In summary, NER1006 is associated with an unprecedented incidence of hypernatremia in FDA approved preparations. This effect results from a high sodium load and an inadequate prescription for free water intake in the clinical trials. Clinicians prescribing NER1006 should understand the potential for hypernatremia and dehydration and encourage at least 2 liters of water or clear liquid intake in addition to the 1 liter of active ingredient. Caution should be exercised in prescribing NER1006 to at-risk populations.

Sincerely,

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Table 1. Incidence of hypernatremia and dehydration related outcomes in the randomized trials of NER 1006

	NOCT		**MORA**			**DAYB**	
	NER1006*	Trisulfate*	NER1006*	NER1006**	PEG-ELS Ascorbate (Moviprep)*	NER1006+	SP-MC+
Number of patients	262	265	262	269	263	235	241
Elevated serum sodium	39.3%	4.2%	13.4%	17.5%	0	NS	NS
Elevated serum chloride	20.6%	1.5%	17.2%	21.6%	2.3%	NS	NS
Dehydration	6(2.3%)	1(0.4%)	1(0.4%)	4(1.5%)	1(0.4%)	3(1.3%)	0
Nausea	16(6.1%)	4(1.5%)	12(4.6%)	13(4.8%)	9(3.4%)	6(2.6%)	2(0.8%)
Vomiting	13(5.0%)	5(1.9%)	10(3.8%)	17(6.3%)	3(1.1%)	11(4.7%)	0
Treatment emergent adverse events related to study agent	39(14.9%)	25(9.4%)	30(11.5%)	40(14.9%)	20(7.6%)	28(11.9%)	10(4.1%)

*Administered as split-dose (evening before and morning of colonoscopy)

**Both doses administered on the day of colonoscopy

+ Both doses administered the evening before colonoscopy

NS: Not stated

Table 2. Summary/Recommendations from the consulting nephrologist (published with permission of Salix Pharmaceuticals)

- There is a rise in Na in 39% of patients (average 141-144). This is not clinically significant in itself, but patients already at risk could develop hypernatremia with use of the bowel prep.
- The rise in Na most likely results from an approximately equal volume of fecal water excretion with decreased water intake, resulting in net dehydration of 1L free water.
- A rise in Na above 145 is associated with increased mortality in multiple patient population study groups and the risk should be taken seriously, although it is not well established to what degree this is causative versus associative.
- Groups at increased risk for hypernatremia include geriatric patients, patients with diminished thirst mechanism or poor access to water, patients with impaired mental status, patients taking diuretics, chronic kidney disease (particularly with a GFR <60), particularly patients with medullary disease (polycystic kidney disease, medullary cystic disease, tubular disorders), patients with diabetes insipidus, or patients taking medications or with conditions that would cause an osmotic diuresis (ie, mannitol, hyperglycemia), pediatric patients, patients with acute kidney injury, or ICU patients.
- NER1006 is a novel bowel prep with features and benefits (low volume, pleasant taste) that are of clinical value. In a number of large, randomized, clinical trials, the product was found to be safe and effective. Hypernatremia was identified in a proportion of patients taking NER1006 at a higher rate than comparators. As a general precaution I would recommend the encouragement of **additional** free water intake for patients who take NER1006, particularly in the patient populations identified above that might be at increased risk; this should help to ensure that hypernatremia would probably be avoided.